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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,410	08/04/2003	Stevan P. Tofovic	007278-10	6070

36234 7590 10/02/2007

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EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
10/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,410	TOFOVIC ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's remarks filed on 7/23/2007 have been fully considered. Applicant's arguments over the 35 USC 112, first paragraph rejection have been fully considered and are not found persuasive. Applicant argues that the specification teaches a procedure for treating rats with nephrotoxicity (induced by PAN) with 2-OHE and that 2-OHE reduced the PAN-induced mortality rate by 66% and that one would understand that treating rats with 2-OHE prevented kidney disease and subsequent death. This argument is not found persuasive because if 2-OHE prevented kidney disease and death, it would totally abolish either from ever occurring. Instead, as Applicants point out in their remarks and in the specification, administration of 2-OHE reduced PAN-induced mortality by 66%, meaning that some PAN-induced mortality still occurred and a total prevention did not occur.

Applicants further argue that PAN induces proliferation of glomerular mesangial cells and 2-OHE inhibits this effect. In response to this argument, and as explained in the specification and the drawings, 2-OHE reduced the proliferation of glomerular mesangial cells but did not completely abolish it. Applicant further argues that PAN induces glomerular and interstitial infiltration of inflammatory cells and this is attenuated by 2-OHE and PAN expands the extracellular matrix in the glomerular and this is attenuated by 2-OHE as well. In response to this argument, and as explained in the specification and the drawings, 2-OHE reduced the number of inflammatory cells in glomeruli but did not completely prevent it. In addition, treatment with 2-OHE

significantly decreased PAN-induced increases in collagen but did not prevent the PAN-induced increases.

Applicants disagree with the statement from the Office Action that there are no working examples presented in the specification showing how to prevent nephropathies. As explained in the previous paragraphs and in the Office Action, there is only data exemplifying an attenuation of PAN-induced renal damage. In response to Applicants arguments that one would not need to undertake undue experimentation to practice the instant invention, it is again pointed out that the specification fails to teach prevention of nephropathies, it only teaches treatment. Therefore, there would be undue experimentation to practice the instant invention as claimed.

Applicant's arguments over the 35 USC 103 rejections have been fully considered and are not found persuasive. Applicants argue over the 35 USC 103 rejection over Tofovic et al. (J Am Soc Nephrol 12: 86A, 2001) that Tofovic et al. does not specifically teach that the conditions being treated are drug-induced or the prevention of such drug-induced conditions. Applicants further say that Tofovic et al. does not contain an incentive to modify its teachings in order to treat the drug-induced conditions of the instant application. In regards to the argument of prevention, see the above remarks. In as far as addressing that the conditions are not drug-induced, the Examiner would like to point out that all of the conditions are associated with nephropathies regardless of how they originated; therefore, it is obvious that the teachings of Tofovic et al. would necessarily treat nephropathies regardless of it is drug-induced or naturally occurring. Applicants make arguments regarding the 35 USC 112,

second paragraph rejection, which was addressed above. Applicants point out that it was stated in the rejection that this case involves "an unpredictable and undeveloped art" and Applicants fail to see how a person would have a reasonable expectation of success in modifying Tofovic et al. to treat or prevent the drug-induced conditions of the instant application. In response to this, the statement made in the 35 USC 112, second paragraph rejection is addressing the claim limitation of "prevention" and not the case as a whole. Tofovic et al. also teach treatment of nephropathies; therefore, it would be obvious that the treatment would be effective regardless of how the condition originated.

Applicants argue that Xiao et al. teaches that estradiol stimulates endothelial ell-derived NO synthesis and that decreased NO synthesis is associated with the pathogenesis of renal disease. As noted by Applicant, this information relates to estradiol and not its metabolites. Further Xiao et al. state this as a hypothesis. Xiao et al. does teach that the metabolites are effective at inhibiting GMC growth by inhibiting DNA synthesis, collagen synthesis, and cell proliferation (second paragraph, Figures 4 and 5) and the authors conclude that the metabolites may prevent glomerulosclerosis by the inhibition of abnormal growth of GMC's. Therefore, it is evident that the metabolites are acting via a different mechanism than estradiol but are more effective in inhibiting growth of GMC's.

Applicant's argues that the 35 USC 103 rejection over Tofovic et al. and Xiao et al. in view of Allison et al. (U.S. Pg-Pub 2006/0083778) is not valid because Tofovic et al. and Xiao et al. do not teach every element of the claim. Those arguments have been addressed above and the rejections are being maintained herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating nephropathies, namely nephrotoxicity, does not reasonably provide enablement for **prevention** of kidney disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention: The rejected claims 1-21 are drawn to a method for preventing or treating drug-induced nephrotoxicity, proteinuria, decreases in

glomerular filtration rate, infiltration of inflammatory cells into renal tissue, excessive proliferation of renal cells, and excessive extracellular matrix protein production comprising administration of an estradiol metabolite.

(2) The state of the prior art: The state of the art regarding treating the various listed nephropathies is relatively high (see review article by Snyder, S. "Detection and evaluation of chronic kidney disease" Am Fam Physician 2005; 72: 1723-32). However, the state of the art for prevention of nephropathy is underdeveloped.

(3) The relative skill of those in the art: The relative skill of those in the art is high.

(4) The breadth of the claims: The claims 1-21 embrace preventing or treating drug-induced nephropathies comprising administration of an estradiol metabolite.

(5) The amount of guidance or direction presented: In the instant case, no working examples are presented in the specification as filed showing how to prevent nephropathies. Note that lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP § 2164. The specification on pages 11-20 details studies performed in rat models administered puromycin aminonucleoside (PAN) to induce nephrotoxicity. Of these animals, one group was administered 2-hydroxyestradiol, which attenuated the PAN-induced renal damage.

(7) The presence or absence of working examples: Applicant does not provide any working examples for the prevention of nephropathy.

(8) The quantitation of experimentation necessary: Claims 1-21 read on the prevention of nephropathies as discussed above, the specification fails to provide sufficient support for completely protecting against nephropathies. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. "Renoprotective effects of 2-hydroxyestradiol", *J Am Soc Nephrol* 12: 86A, 2001.

Tofovic et al. teach that chronic treatment with 2-hydroxyestradiol (2-OHE) significantly reduced symptoms of nephropathy, such as proteinuria (meeting the limitations of claims 5-6 and 8), glomerulosclerosis (meeting the limitation of claims 9-10 and 12), and interstitial inflammation (meeting the limitation of claims 13-14 and 16) in male obese rats, which is a model of nephropathy (see entire abstract).

Regarding the conditions cited in claims 1, 2, 9, 13, 17, and 21, it is considered that these conditions are all associated with nephropathy; therefore, it is obvious that the teachings of Tofovic et al. would treat the conditions listed in the above claims.

Tofovic et al. does not teach that the conditions listed in claims 1, 2, 9, 13, 17, and 21 are drug-induced; however, these pathologies of the kidney would display the same symptoms regardless of if it is drug-induced or a natural occurrence, so the treatment with estradiol metabolites would have the same results. One having ordinary skill in the art would have been motivated to extend the teachings of Tofovic et al. to treat various forms of nephropathies with estradiol metabolites because the prior art teaches that an estradiol metabolite is effective at treating various types of nephropathies.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xiao, S. et al. "Effects of estradiol and its metabolites on glomerular endothelial nitric oxide synthesis and mesangial cell growth", Hypertension, 2001; 37; 645-650.

Xiao et al. teach that the growth of glomerular mesangial cells (GMC) is associated with the pathogenesis of renal diseases (Pg. 645, second paragraph). It is further taught that estradiol and its hydroxy and methoxy metabolites inhibit glomerular mesangial cell (GMC) growth by inhibiting DNA synthesis, collagen synthesis (meeting the limitations of claims 21-22 and 24), and cell proliferation (meeting the limitations of claims 17-18 and 20; pg. 647, second paragraph and Figures 4 and 5). The authors conclude that estradiol metabolites may prevent glomerulosclerosis by this inhibition of abnormal growth of GMC's (further meeting the limitation of claims 9-10 and 12; pg. 648, first paragraph). It is further taught that the hydroxy and methoxy metabolites of estradiol are more potent than estradiol at inhibiting the growth of GMC's (pg. 647, second paragraph and Figures 4 and 5).

Regarding the conditions cited in claims 1, 2, 9, 13, 17, and 21, it is considered that these conditions are all associated with nephropathy; therefore, it is obvious that the teachings of Tofovic et al. would treat the conditions listed in the above claims.

Xiao et al. does not teach that the conditions listed in claims 1, 2, 9, 13, 17, and 21 are drug-induced; however, these pathologies of the kidney would display the same symptoms regardless of if it is drug-induced or a natural occurrence, so the treatment with estradiol metabolites would have the same results. Because the prior art teaches that estradiol metabolites are renoprotective in cells modeling renal pathogenesis, one having ordinary skill in the art would have been motivated to extend the findings of Xiao et al. to *in vivo* models of nephropathies to evaluate the renoprotective effects of these compounds.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 7, 11, 15, 19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. and Xiao et al. as applied in the above rejections and in view of Allison et al. (U.S. Pg-Pub 2006/0083778).

Tofovic et al. and Xiao et al. do not teach a controlled release formulation.

Allison et al. teach sustained release formulations of estradiol metabolites, including 2-hydroxyestradiol, 2-methoxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol (meeting the limitations of claims 3, 7, 11, 15, 19, and 23; paragraph 0007, 0008, 0010).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Tofovic et al. and Xiao et al., which teach that estradiol metabolites induce renoprotective effects with Allison which teaches sustained drug delivery of estradiol metabolites. One having ordinary skill in the art would have been motivated to formulate controlled release delivery of estradiol metabolites in an extended release drug delivery device to maintain therapeutic blood levels.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is 571-272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER